Medical Progress

Advances in Diagnosis and Management of Salivary Gland Diseases

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Salivary glands may be involved in a wide variety of diseases, which may be broadly grouped into (1) inflammatory, (2) noninflammatory, nonneoplastic and (3) neoplastic categories.

Most inflammatory and noninflammatory, nonneoplastic diseases should be managed conservatively and symptomatically. The common exceptions are first-arch branchial-cleft cysts and calculi.

Neoplastic lesions always require resection if that is feasible. For benign tumors, simple excision with a cuff of normal tissue around it will usually suffice. The prevailing trend for treatment of malignant neoplasms is conservatism. No longer is the facial nerve routinely sacrificed. The resection done is dictated by the tumor size and the facial nerve is spared unless directly invaded. Postoperative radiation therapy is increasingly used.

(Rice DH: Advances in diagnosis and management of salivary gland diseases [Medical Progress]. West J Med 1984 Feb; 140:238-249.)

This review is intended to be an update on current concepts of the diagnosis and management of nonneoplastic diseases of the salivary glands. In addition, there is an extremely brief review of general principles in the management of neoplastic lesions.

The embryology, microscopic and gross anatomy, physiology and biochemistry are briefly reviewed. The importance of saliva in the health of the teeth and mucosa is discussed as well as its antibacterial, antiviral activity.

Embryology

The embryology of the salivary glands is incompletely understood. The major salivary glands and the minor glands anterior to the anterior tonsillar pillars are believed to be derived from ectoderm, whereas the remaining glands are derived from endoderm. Regardless, there is no histologic difference between the two areas and no difference in the tumors that occur there.

Histology

The mature salivary gland unit begins as a serous, mucous or mixed acinus. Each acinus empties into an intercalated duct, which leads to a striated duct that empties into an excretory duct. Each segment has specialized functional and morphologic characteristics.

Acinar cells are highly differentiated cells responsible for the production of mucinous or serous secretions. Parotid acini are predominantly or exclusively serous, whereas submandibular acini are of a single type called seromucous.[1] The mucous acini of the sublingual gland resemble those of the submandibular gland.

The cuboidal cells of an intercalated duct are relatively unspecialized. The striated duct cells are well differentiated and have features that are similar to renal proximal tubule cells. The striated duct cells play an important role in electrolyte and water transportation. The basal cells of the intercalated and excretory ducts act as reserve cells for the most differentiated cells of the salivary gland unit. These reserve cells are responsible not only for normal salivary gland development but also for tumor formation.[2] It is now generally agreed that salivary gland tumors arise from one of these two cells, and data from both light and electron-microscopic studies support this theory.[3]

Gross Anatomy

The parotid gland is the largest salivary gland and lies anterior and inferior to the ear. It overlies the

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upper quarter of the sternocleidomastoid muscle and the masseter muscle.

The submandibular gland occupies most of the submandibular triangle. The inferior surface lies adjacent to the anterior and posterior bellies of the digastric muscle. Anteriorly the gland lies directly on the mylohyoid muscle. The sublingual gland lies below the mucosa of the floor of the mouth anteriorly, superficial to the mylohyoid muscle.

Physiology

The secretory unit of a salivary gland is composed of an acinus, an intercalated duct and a striated duct. Acinar cells are arranged around a central lumen and have contractile myoepithelial cells interposed between them and the basement membrane peripherally. Serous cells produce a watery secretion containing neural carbohydrates; mucous cells secrete a viscous solution with mucopolysaccharides; seromucous cells secrete both. Protein is synthesized by the ribosomes on the endoplasmic reticulum and is transported first to the cisternae of the endoplasmic reticulum and then to the Golgi apparatus. The latter is the site of carbohydrate synthesis and plays a key role in the elaboration of mucus. In serous cells, the secretory granules discharge their contents by establishing a continuity between membranes of a granule and the apical cell surface. For mucous cells, secretory granules are discharged through gaps in the cell surface.

Secretion is controlled by physical and psychic stimulation mediated through the autonomic nervous system. Physical stimuli from the oral cavity and psychic stimuli from taste, smell or sight centers travel afferent pathways to the superior and inferior salivatory nuclei. Both sympathetic and parasympathetic pathways are involved. The control of secretion is complex (Table 1). Parasympathetic and sympathetic innervation affects acinar cells differently, and the α- and β-adrenergic innervation may also have different effects. The autonomic innervation also affects the duct cells, which are involved in the active transport of electrolytes.

Biochemistry

Numerous factors influence the composition of saliva. The collection technique itself will produce either whole saliva or the secretions of a single gland, and either stimulated or unstimulated saliva. The use of whole saliva in which a person expectorates into a container is not ideal, because it is impossible to accurately determine the flow rate that alters the concentration of many constituents and because it is contaminated by desquamated cells, food particles, bacteria and other debris.

The salivary flow rate is variable. There is a diurnal variation with reduced production in the early morning and increased production in the afternoon.[4] The rate is near zero during sleep, but may reach 4 ml a minute during maximal stimulation. The average volume per day has not been well studied and is difficult to measure accurately. The measured volume per day in two patients with esophageal-cutaneous fistulas averaged 500 ml.[5] These patients, of course, were not eating.

The specific gravity of saliva varies from 1.000 to 1.010, increasing with faster flow. The relative viscosities after stimulation are as follows: parotid, 1.5, submandibular, 3.4, and sublingual, 13.4 centipoises.[6] The viscosity is directly related to the percentage of mucous cells. The pH is slightly acidic before secretion into the oral cavity, but becomes slightly alkaline on entering the oral cavity due to the loss of carbon dioxide. Because the bicarbonate concentration increases with rising flow rate, the pH becomes elevated at high flow rates. About 90% of the total volume of saliva comes from the parotid and submandibular glands in about equal amounts.

The mean concentrations of some of the substances found in saliva are shown in Table 2. The flow rate can significantly alter some of these values in that as it increases, sodium and bicarbonate levels and pH rise, while potassium, calcium, phosphate, chloride, urea and protein levels fall.

Other factors influence the composition of saliva independently of the flow rate (Table 1). A high-

TABLE 1.—*Factors Affecting Flow Rate and Composition of Saliva*

Drugs	
	Cocaine, strychnine, reserpine, morphine, digitalis, quinidine, muscle relaxants, anti-parkinsonism drugs, theophylline, sympathetic and parasympathetic drugs
Loss of Functioning Gland Substance	
	Irradiation, aplasia, chronic inflammation, ductal obstruction
Hormonal Changes	
	Cushing's disease, Addison's disease, aldosteronism, menstruation, pregnancy
Mucous Membrane Irritation	
	Smoking, quinine, peppermint
Disrupted Fluid and Electrolyte Balance	
	Diabetes insipidus, diuretics, dehydration, uremia

TABLE 2.—*Composition of Saliva*

	Salivary Gland	
Substance	*Parotid mEq/liter*	*Submandibular mEq/liter*
Potassium	20.0	17.0
Sodium	23.0	21.0
Chloride	23.0	20.0
Bicarbonate	20.0	18.0
Calcium	2.0	3.6
Magnesium	0.2	0.3
Phosphate	6.0	4.5
	mg/dl	*mg/dl*
Urea	15.0	7.0
Proteins	250.0	150.0
Ammonia	0.3	0.2
Uric acid	3.0	2.0
Lysozymes	2.3	1.5
Glucose	<1.0	<1.0
IgA	4.0	2.0
Amylase	0.1	0.0025
Cholesterol	<1.0	unknown
pH	5.92	5.73

protein diet increases the urea concentration. The sodium concentration is altered by aldosterone, glucocorticoids and adrenocorticotropic hormone. The concentrations of iodide, calcium and bicarbonate depend on the plasma concentration. The concentrations of urea and uric acid are related to the blood levels, and the effectiveness of hemodialysis can be followed by parotid salivary analysis.[7]

Amylase is the main protein in parotid saliva. The major protein constituents of the more mucus-secreting glands are the glycoproteins, especially sialic acid. About 75% of people secrete a glycoprotein named blood group substance in their submandibular and sublingual saliva. Blood group substance is responsible for blood type, and thus blood type can be determined in secretors by salivary analysis. Another glycoprotein produced by the parotid and submandibular glands is secretory piece, which binds two molecules of immunoglobulin A to stabilize this IgA and form secretory IgA.

Function of Saliva

The composition of saliva endows it with several important physical and biochemical properties. The mucous layer protects the oral mucosa from local irritants and from desiccation. Further, the mucus takes a relatively direct and constant course in the oropharynx, sweeping microorganisms and foreign particles with it for destruction and elimination by the gastrointestinal tract.[8] The glycoproteins in saliva lubricate the tongue, oral mucosa and teeth to facilitate speaking and swallowing.

Saliva protects the teeth. The lubricating function reduces wear. The minerals aid in posteruption maturation and calcium and phosphate help prevent enamel dissolution in plaque. Bicarbonate and phosphate exert antibacterial activity within plaque by their buffering capacities.

The importance of saliva in protecting teeth is well illustrated by the pronounced increase in caries seen following radiation therapy to the oral cavity. Irradiation causes a great reduction in salivary flow rate—95% and more after full-course radiation therapy—and this reduction persists indefinitely.[9,10] Morphologic studies have shown that serous acini are destroyed, whereas there is little discernible change in the mucous acini.[11] Because of this, the composition is also changed with increased concentrations of sodium, chloride, calcium and protein and a decrease in bicarbonate.[12]

Antibodies are found in saliva. Secretory IgA does not fix complement, but appears able to agglutinate bacteria, making them more readily phagocytized. Some investigators have found elevated levels of IgA in caries-resistant patients, while others have not.[13,14] Small amounts of IgG and IgM are also present, and raised levels have been found in patients with periodontitis or oral candidiasis. However, patients with hypogammaglobulinemia do not have an increased incidence of caries or gingivitis,[15] so the practical significance of these antibodies is uncertain.

Lysozymes are found in the saliva of all major glands They are formed or concentrated in the basal cells of the striated ducts. The lysozymes from different glands have different structures, but all act as a muramidase by hydrolyzing glycopeptides containing muramic acid in bacterial cell walls.[16] Lactoferrin is an iron-binding protein in saliva that may inhibit bacterial growth by denying them iron.[17] Lactoperoxidase with hydrogen peroxide and thiocyanate ion (the so-called thiocyanate-dependent factors) can inhibit lactobacillus, cariogenic streptococci and, perhaps, coliforms.[18] There is disagreement about the existence of

TABLE 3.—*Causes of Xerostomia*

Cause	*Incidence*
Local	
Candidiasis	6
Miscellaneous	6
Systemic	
Sjögren's syndrome	35
Drugs	25
Anemia	6
Endocrine	3
Idiopathic	19

TABLE 4.—*Changes in Saliva in Disease*

Variation From Normal	*Salivary Flow and Composition*
Dehydration, fatigue, infection, psychopathic emotional states, use of tranquilizers	↓ flow rate
Cigarette smoking, schizophrenia, acute stomatitis, heavy metal poisoning, rabies, pernicious and iron-deficiency anemia	↑ flow rate
Primary aldosteronism	↓ sodium, normal potassium
Cushing's disease	↓ sodium, normal potassium
Addison's disease	↑ sodium, normal potassium
Pregnancy	↓ sodium, ↑ potassium
Cystic fibrosis	↑ calcium, protein, amylase
Hyperparathyroidism	↑ calcium, phosphorus
Essential hypertension	↓ sodium and flow rate
Sarcoidosis	↓ amylase, kallikrein ↑ albumin, lysozyme
Acute pancreatitis	↑ amylase
Alcoholic cirrhosis	↑ potassium, amylase, flow rate
Irradiation	↑ sodium, chloride, calcium, protein ↓ bicarbonate

↓ = decreased, ↑ = increased

a bacteriolytic substance in the saliva of caries-free persons.[19-21] A substance named nerve growth factor exists in saliva that greatly stimulates nerve tissue growth. Its level has been reported to be raised in the serum of children with neuroblastoma.[22]

Changes in Saliva in Disease

Dehydration, admission to hospital, mental stress, psychopathic emotional states, fatigue, infection, raised ambient temperature, tranquilizers, ganglionic blockers and light deprivation decrease salivary flow. Cigarette smoking, acute stomatitis, heavy metal poisoning, acrodynia, rabies and the ingestion of highly seasoned foods increase flow. Chewing on one side of the mouth increases the flow on that side.

Xerostomia may be primary or secondary, and the causes are numerous. It is usually not a problem until the flow rate is less than 0.2 ml per minute per gland. In addition to the previously mentioned causes, pernicious and iron-deficiency anemia and loss of salivary tissue (as from irradiation, infection or Sjögren's syndrome) cause decreased flow. Most causes of xerostomia are systemic in nature, but a significant percentage are idiopathic (Table 3).

Many diseases affect salivary composition (Table 4). Primary aldosteronism causes a decreased sodium level with normal potassium content. It has been suggested that a sodium-potassium ratio of 0.3 or less is diagnostic, below 0.5 is suggestive and above 1.0 rules out aldosteronism (normal, 1.3).[23] Low sodium-potassium ratios are also found in Cushing's disease with a mean ratio of 0.5.[24(p115)] High ratios occur in Addison's disease with a mean ratio of 5.0. In pregnancy, the submandibular calcium concentration is reduced, whereas the sodium concentration is reduced and the potassium concentration is increased in both parotid and submandibular saliva.[25]

The salivary glands, like the other exocrine glands, are affected by cystic fibrosis. The submandibular saliva is thickened by increased amounts of calcium and calcium-precipitable proteins, with no change in viscosity.[26] Total protein, amylase, lysozyme and glycoprotein concentrations are increased in submandibular but not in parotid saliva.[27] There is no change in the flow rate in the major glands,[28] but there is a significant reduction in the minor glands.[29]

Thyroid diseases and their treatment may affect the saliva. The salivary glands concentrate iodine to 40 times the plasma level, regardless of the thyroid-stimulating hormone level or the state of thyroid function.[30] Hyperparathyroidism causes an increased amount of calcium and phosphorus in saliva, with the levels paralleling the parathormone levels.[31] In cases of essential hypertension, the sodium concentration and the flow rate are decreased.[32] In sarcoidosis, amylase and kallikrein levels are decreased, whereas albumin and lysozyme concentrations are increased.[33,34] Acute pancreatitis may cause an increase in the amount of amylase. Alcoholic cirrhosis may cause an increased flow rate with increased concentrations of potassium and amylase.[35] Salivary flow rate is decreased by depression and increased by schizophrenia.[36]

Inflammatory lesions may cause changes in saliva. In acute infections, the sodium and potassium levels approach those of serum.[37] There is also a pronounced decrease in phosphate concentration. Other elements that are increased in amount include glucose, IgA, IgG, IgM, albumin and transferrin, which leak from plasma, and myeloperoxidase, lactoferrin and lysozyme, which are produced by the inflammatory infiltrate. IgG dominates the immunoglobulins, reflecting the normal serum pattern rather than the normal salivary pattern, in which IgA dominates.

Irradiation causes pronounced changes in saliva, the most obvious being a severe reduction in flow rate. Flow rates are reduced 95% or more after full-course radiation therapy and this reduction persists indefinitely.[9,10] Histopathologic studies have shown that the parotid acini and the serous cells from the submandibular gland are severely injured, but there is little discernible change in the mucous cells. The composition is also altered, with increased amounts of sodium, chloride, calcium and protein and a decrease in bicarbonate. These changes lead to a significant rise in the number of dental caries.

Numerous systemically administered drugs can be detected in saliva, including iodide, heavy metals, thiocyanate, morphine, clindomycin and rifampin.[38] Digitalis toxicity causes greatly elevated levels of potassium and calcium, and this study can be used to distinguish between toxic and therapeutic doses.[39]

Inflammatory Disorders

Acute Suppurative Sialadenitis

Acute suppurative sialadenitis may involve the parotid or submandibular gland, with the vast majority of cases showing parotid involvement. The parotid gland is felt to be more susceptible because parotid saliva has less bacteriostatic activity than submandibular saliva.[40] Presumably this is because the bacterial aggregating ability—and thus eliminating ability—is greater with the high-molecular-weight glycoproteins in the mucous acini and the other antibacterial systems seem the same.[41]

Acute suppurative sialadenitis accounts for about 0.03% of hospital admissions.[40,42] About 30% to 40% of cases occur after an operation, with the highest incidence following gastrointestinal tract procedures, usually with an onset three to five days postoperative. The primary pathogenic event is thought to be salivary stasis, either from obstruction or from decreased production. Predisposing conditions include calculi, duct stricture, dehydration and poor oral hygiene. These conditions most frequently exist in an in-hospital patient who has reduced resistance and is receiving multiple medications that alter oral flora.[42] When, in addition, a patient is not eating, salivary flow is further reduced. An ascending bacterial infection occurs and leads to suppuration within the gland. This complication occurs in 1 in 1,000 to 2,000 operative procedures.

It occurs most frequently in the sixth and seventh decades, though it has been reported for all ages.[43] The sex distribution is equal.

The classic clinical presentation is a debilitated or postoperative patient in whom a diffuse enlargement of a parotid gland develops, with associated induration and tenderness. Purulent saliva can be expressed from the duct orifice and it occurs on both sides in 20% of cases.[44] A specimen of the purulent saliva should be cultured for aerobic and anaerobic bacteria and a Gram's stain done. The offending organism is usually coagulase-positive *Staphylococcus aureus*. Other occasionally implicated aerobic organisms include *Streptococcus pneumoniae, Escherichia coli* and *Haemophilus influenzae*.[45] Anaerobic organisms include *Bacteroides melaninogenicus* and *Streptococcus micros*.[46] On microscopic examination there is glandular destruction with abscess formation and erosion of the ducts with penetration of the exudate into the parenchyma.

Initial treatment consists of adequate hydration, good oral hygiene, repeated massage of the gland and antibiotics given intravenously. While awaiting culture results, empiric administration of a penicillinase-resistant, antistaphylococcal antibiotic is advisable, if the Gram's stain shows Gram-positive cocci. Mortality rates approach 20%,[47] though much of this is probably because it occurs in already seriously ill patients. Therefore, if a response to the appropriate treatment regimen does not occur quickly, incision and drainage should be done. This is carried out by raising a parotid flap as for a parotidectomy and then, using a hemostat, making multiple openings into the gland, spreading the hemostat in the general direction of the facial nerve. Following this, a drain is placed over the gland and the wound closed. Successful needle aspiration guided by ultrasound has been reported, and the use of new computed tomographic (CT) scanners should be equally feasible.

Chronic Recurrent Sialadenitis

The primary pathogenic event in chronic sialadenitis is believed to be a decreased secretion rate with subsequent stasis. Two theories of initiation are currently espoused. One is that repeated acute episodes or a single severe episode of suppurative sialadenitis leads to ductal metaplasia to mucus-secreting glands. This leads to an increased mucous content in the saliva, which contributes to the salivary stasis. The other theory is that if a gland is colonized by pyogenic bacteria, an acute suppurative infection will result, whereas colonization with opportunistic oral flora will lead to chronic, recurrent sialadenitis.

This disease is much more common in the parotid gland, presumably because of its longer, narrower duct,[48] making it more susceptible to stasis. Regardless of the cause, as time passes, the disease leads to sialectasis, ductal ectasia and progressive acinar destruction with an associated lymphocytic infiltrate. The lymphocytic infiltrate is a response to ductal and acinar damage, with progressive replacement of secreting glandular elements by the infiltrate.

This progressive glandular destruction causes several changes in the chemistry of saliva. There are increased amounts of sodium and protein[49(p344)] with a pronounced decrease in phosphate level. Also increased are IgA, IgG, IgM, albumin, transferrin, myeloperoxidase, lactoferrin and lysozyme. The IgG dominates the immunoglobulins, reflecting the serum pattern rather than the usual salivary pattern in which IgA dominates.

Clinically there is recurrent, mildly painful parotid enlargement, usually associated with eating. Physical examination confirms this, and massage of the gland often produces scanty saliva. In 80% of patients permanent xerostomia develops. Treatable predisposing factors, such as a calculus or a stricture, should be investigated and, if found, treated appropriately. If none is found, treatment should otherwise be conservative, involving the use of sialagogues, massage and administration of antibiotics during acute suppurative exacerbations. If conservative measures fail—and this is unusual—other treatment options include periodic ductal dilatation, ligation of the duct, total gland irradiation, tympanic neurectomy and excision of the gland. All of these options, except the last, work occasionally, but not uniformly. Ligation of the duct may successfully cause atrophy of the gland but sometimes results in an acute infection or in a mucocele. Irradiation produces an initial acute inflammatory reaction, but continued treatment results in destruction of the gland. This should only be considered in older patients, in whom the risk of irradiation-induced carcinoma is reduced. If all else fails, excision of the gland is curative.[50]

Recurrent parotitis may also occur in children. Unlike the adult form, this entity afflicts more male children than female children. The underlying cause is unproved, but the disease begins with the sudden onset of either unilateral or bilateral parotid swelling. Attacks may be single or recurrent, with varying degrees of enlargement during and between acute episodes. Saliva may be clear or flocculent and the flow rate decreased. Salivary chemistry levels are altered, as in adult patients.

Clinically an affected child is usually not ill, though there may be a mild rise in the temperature and the leukocyte count. Mild pain may be present, but a child will not have xerostomia.[51] The disease may disappear at puberty or continue into adulthood.

Benign Lymphoepithelial Lesion

The benign lymphoepithelial lesion belongs in a spectrum of diseases characterized by a lymphoreticular infiltration into the gland, combined with acinar atrophy and ductal metaplasia ending in the epimyoepithelial island.[52] Histologically there is chronic inflammation, with variations being related only to distribution and severity. Some regard this lesion as "end-stage" chronic recurrent parotitis. Other diseases within

this spectrum include primary and secondary Sjögren's syndrome. Unlike these, however, the benign lymphoepithelial lesion usually affects only a single salivary gland and is less predominant in women.

The usual clinical feature is asymptomatic enlargement of a single salivary gland. Superimposed infection may occur and should be treated as an acute sialadenitis. If the lesion is asymptomatic and is not cosmetically objectionable, no treatment is necessary.

Of considerable concern are occasionally seen benign lymphoepithelial lesions that evolve into more aggressive lesions. As of 1980, there had been reported evolution of the disease into 84 cases of lymphoproliferative disease, 27 cases of carcinoma and 12 cases of pseudolymphoma. The lymphoproliferative disorders are virtually all histiocytic or lymphocytic lymphoma involving extrasalivary sites. The sudden development of hypogammaglobulinemia or leukemia may herald the onset of lymphoma. The carcinoma is usually salivary and usually anaplastic. Many patients have been of Indian or Eskimo extraction, but this may represent merely a reporting artifact. These entities should be watched for and treated early and aggressively when they occur.

Sjögren's Syndrome

Sjögren's syndrome is characterized by a lymphocyte-mediated destruction of the exocrine glands leading to xerostomia and keratoconjunctivitis sicca. It is the second most common autoimmune disease after rheumatoid arthritis.[53] The average age by onset is 50 years and 90% of cases occur in women.

The clinical manifestations were first described by Hadden in 1888.[54] Four years later, Mikulicz published a single case report of a patient with bilateral lacrimal, parotid and submandibular gland swelling.[55] In 1933 Sjögren, a Swedith ophthalmologist, published a classic monograph on the disease, emphasizing its systemic nature.[56] Sjögren's syndrome occurs in two forms—primary, which involves exocrine glands only, and secondary, which is associated with a definable autoimmune disease, usually rheumatoid arthritis.[57]

Sjögren's syndrome generally runs a relatively benign course of primarily exocrine gland dysfunction. This leads to burning oral discomfort and a "sandy" sensation in the eye. Either unilateral or bilateral salivary gland swelling, usually involving the parotid, occurs in 80% of primary and 30% to 40% of secondary cases. The swelling may be intermittent or permanent. Arthritis is the most frequent initial symptom in secondary Sjögren's. Recent studies have shown that there are genetic differences between primary and secondary Sjögren's syndrome.[58,59]

Associated symptoms are numerous and include interstitial pneumonitis, dryness of the skin, Raynaud's phenomenon, achlorhydria, hepatosplenomegaly, genital dryness, hyposthenuria, myositis and pancreatitis. Patients with primary Sjögren's have a greater incidence of recurrent parotitis, Raynaud's phenomenon, purpura, lymphadenopathy, myositis and renal involvement than do those with secondary Sjögren's.[60]

TABLE 5.—*Autoantibodies in Sjögren's Syndrome*

Autoantibody	*Incidence Percent*
Rheumatoid factor	70-90
Antinuclear antibody	55-70
Salivary duct antibody	65
Parietal cell antibody	27
Thyroglobulin antibody	18
Thyroid microsomal antibody	21

TABLE 6.—*Sialochemical Values in Sjögren's Syndrome*

Parameter	*Sjögren's*	*Controls*
Flow rate (ml/min)	0.17	0.58
Sodium (mEq/liter)	65.0	23.0
Chloride (mEq/liter)	64.0	23.0
Potassium (mEq/liter)	20.0	22.0
Phosphate (mEq/liter)	2.3	6.3
Calcium (mEq/liter)	1.9	2.1
Urea (mEq/liter)	9.8	10.5
Total protein (mg/dl)	252.0	236.0
IgA	5.8	3.6
IgG	1.0	0.5
Albumin	1.3	0.8
Amylase (units/ml)	1,480.0	1,440.0

A number of laboratory findings suggest that one of the underlying defects in Sjögren's syndrome is B-cell hyperreactivity, with or without abnormalities of immunoregulation. These include polyclonal hypergammaglobulinemia, numerous autoimmune antibodies—both organ- and nonorgan-specific—and circulating IgG immune complexes.[61,62] The relative frequency of some antibodies is shown in Table 5. In addition, elevated levels of antibody to secretory IgA have been reported.[63]

Sialographic abnormalities parallel the clinical and histological severity of the disease, with a characteristic finding being one of varying degrees of sialectasis. Grossly and histologically the individual salivary gland resembles a gland involved with chronic inflammation. There is ductal ectasia on sialography and lymphoreticular infiltration, acinar destruction and the formation of epimyoepithelial islands. The lymphoreticular infiltration consists largely of small or medium-sized lymphocytes and plasma cell on electron microscopy.[64] Sialochemical studies have shown a number of abnormalities (Table 6). Sodium and chloride concentrations are about three times normal, whereas the phosphate level is one-half normal.[65] The potassium content is usually normal, as is the case in chronic inflammatory disorders. The amylase and total protein concentrations are normal, suggesting that the remaining acinar cells are capable of normal protein synthesis. The greatly reduced flow rate, however, markedly reduces the amount of antibacterial material delivered to the oral cavity. Dental caries are significantly increased.[66]

Sjögren's syndrome, like the benign lymphoepithelial lesion, is associated with an increased incidence of lymphoma. The incidence is increased 44 times over

TABLE 7.—*One Formula for Artificial Saliva*

Reagent	*Volume Grams*
Potassium chloride	2.398
Sodium chloride	3.462
Magnesium chloride	0.235
Calcium chloride	0.665
Potassium phosphate	3.213
Potassium dihydrogen phosphate	1.304
Methyl *p*-hydroxybenzoate	8.0
Flavoring	16.0
70% Sorbitol	171.0
Carboxymethylcellulose sodium	40.0
Sodium fluoride	17.68
FD&C red 40 dye (2%)	1.0 ml
Water q.s. add	4,000.0 ml

the normal and is usually of the histiocytic or mixed histiocytic-lymphocytic type.[67] Half of those in whom a lymphoma develops have had prior irradiation to the parotid. Pseudolymphoma may also occur and, like the lymphoma, has been shown to be of B-cell origin. Sjögren's syndrome has also been associated with biliary cirrhosis, other liver abnormalities, involvement of the larynx, the development of membranous glomerulonephritis, autoimmune liver disease and secondary amyloidosis.[68(p64)]

Treatment is symptomatic. Xerostomia causes a burning oral discomfort, difficulty in eating dry foods and decreased taste sensitivity. Mucosal ulcerations and increased dental caries may occur. The simplest treatment is the use of an artificial saliva swirled in the mouth and swallowed every three to four hours. (Table 7). The salivary glands should be stimulated to produce what saliva they can. Dental hygiene must be impeccable. Acute infections should be treated as acute sialadenitis.

Xerophthalmia is best treated with artificial tears every three to four hours as needed. Taping the lids closed at bedtime is an excellent precaution. Occasionally tarsorrhaphy may be necessary. Care must be taken as corneal ulcerations and perforations have been reported.[69] Patients also have an increased incidence of otitis media, bronchitis, pneumonia, pancreatitis and atrophic gastritis, which should be watched for and treated appropriately.

It has been suggested that an inadequate synthesis of prostaglandin E_1 is the key factor in xerostomia and xerophthalmia, and some success in raising tear and saliva production has been reported by raising the level of prostaglandin E_1 precursors and vitamin C in the diet.[70]

Granulomatous Diseases

Primary tuberculosis of salivary tissue is uncommon. The parotid is most commonly involved, usually on one side only. The infection is felt to arise usually from the tonsils or teeth. It occurs in one of two forms—an acute inflammatory lesion or a chronic tumorous lesion. The former may be a difficult diagnostic problem and the diagnosis may not be made until, faced with a lack of response to conventional antibiotics, acid-fast salivary stain and purified-protein derivative (PPD) tests are done. The PPD may be unreliable as infections caused by atypical mycobacteria are increasing relative to *Mycobacterium tuberculosis hominis*.[71] Treatment is as for any acute tuberculous infection. The chronic tumorous form is usually diagnosed only after excision of the gland for a suspected tumor. This may change with the more widespread use of fine needle aspiration cytologic studies. Excision is curative. Secondary tuberculosis can occur and more commonly involves the submandibular and sublingual glands.

Animal scratch disease may involve the salivary glands, but only by contiguous spread from a lymph node. This is a self-limiting disease and treatment is symptomatic.

Actinomycosis may also occur in the salivary glands. As with actinomycosis elsewhere, treatment involves incision and drainage combined with long-term penicillin therapy.

Sarcoidosis is a granulomatous disease of cryptogenic cause that is a diagnosis of exclusion. Whereas salivary gland involvement occurs in 33% of cases in histologic studies, it is clinically manifest in only 6%.

Uveoparotid fever (Heerfordt's syndrome) is a particular form of sarcoidosis consisting of uveitis, parotid swelling and facial paralysis. It usually occurs in the third or fourth decade and has a prodrome of fever, malaise, weakness, nausea and night sweats lasting several days to several weeks. This may occur with or without other systemic signs of sarcoidosis. Generally both parotids enlarge simultaneously, and submandibular, sublingual and lacrimal involvement may occur. The swelling lasts months to years without suppuration and with eventual resolution. Involvement of the minor salivary glands may occur, and labial biopsy may establish the diagnosis.[72] The sialographic appearance depends on the extent of glandular invasion and ranges from normal to moderate loss of ductal radicals. Scanning using technetium Tc 99m frequently shows abnormalities. Histologic examination shows the expected noncaseating granulomas, which, like tuberculosis, involve the lymphoid tissue more than the parenchyma. Sialochemistry studies show a decreased level of amylase and kallikrein, with an increase in albumin and lysozyme levels. Treatment is symptomatic, with corticosteroids being most useful in the acute phase, particularly for facial paralysis. Even without treatment the facial paralysis is usually transient. Uveitis should be followed closely as it can lead to glaucoma.

Viral Infections

Mumps is by far the most common cause of parotid swelling and is the most common viral agent to involve the salivary glands. It is most commonly recognized in the 4- to 6-year-old age group. The incubation period is two to three weeks, with a clinical onset characterized by pain and swelling in one or both parotids. Systemic symptoms include fever, malaise,

myalgias and headache, and usually resolve before the parotid swelling. Many cases are subclinical, and studies have shown that more than 95% of adults have neutralizing antibodies.[73] A recent epidemiologic study has shown a statistically significant association between mumps and the subsequent rapid onset of childhood diabetes.[74]

Salivary gland inclusion disease is a rare form of cytomegalic inclusion disease. It involves newborns and may cause mental and physical retardation as well as hepatosplenomegaly, jaundice and thrombocytopenic purpura. Other viral agents that may infect the salivary glands include coxsackievirus A, echovirus, influenza A and the virus of lymphocytic choriomeningitis. The treatment in all cases is directed toward symptoms.

Noninflammatory, Nonneoplastic Disorders

Sialolithiasis

Of all salivary calculi, 80% occur in the submandibular gland, whereas less than 20% occur in the parotid and 1% occur in the sublingual gland. Minor salivary gland calculi are uncommon and have a predilection for the upper lip and buccal mucosa.[75]

For the major glands, there is a single calculus in 75% of cases and multiple gland involvement in 3%. Most occur in middle age and there is a slight male predominance. Calculi may occur unassociated with other salivary disease, but also occur in two thirds of cases of chronic sialadenitis. The only systemic disease associated with salivary calculi is gout, and the calculi are then composed of uric acid.

Most calculi are composed largely of calcium phosphate as the hydroxyapatite, with small amounts of magnesium, carbonate and ammonium. The organic matrix is composed of various carbohydrates and amino acids. About 90% of submandibular calculi are radiopaque, but 90% of parotid calculi are radiolucent. Prerequisites for calculus formation are stasis and a nidus of material for the precipitation of salivary salts. There is some evidence that most submandibular calculi arise de novo around a nidus of mucus, whereas parotid calculi are preceded by an inflammatory response and form around inflammatory cells.[76] The submandibular gland is believed to be more susceptible because its saliva is more alkaline, has a greater concentration of calcium and phosphate and has a higher mucus content. In addition, the duct is longer and the flow is antigravity.

Occasionally calculi are asymptomatic or appear as acute suppurative sialadenitis. Usually a patient has had recurrent swelling and pain in the involved gland, usually aggravated by eating. With repeated episodes, infection may intervene. In general, sialoliths within the glandular parenchyma are associated with less severe symptoms than those producing obstruction of the main duct. On physical examination diffuse enlargement and tenderness of the involved gland are found. A calculus is frequently palpable. Calculi within a major duct tend to be smooth, whereas those within the gland tend to be irregular. Massage of the gland shows decreased flow of cloudy, sometimes mucopurulent saliva. For the usual submandibular gland radiopaque calculus, routine mandibular roentgenography suffices for the diagnosis. For parotid calculi, an anteroposterior roentgenogram coupled with an intrabuccal film show a calculus 71% of the time.[77] For either gland, sialography is essentially 100% effective. Ultrasonography may also be used.[78]

Complications of sialolithiasis include acute suppurative sialadenitis and ductal ulceration and stricture. Treatment depends on the location of the calculus; if it is near the duct orifice, intraoral removal is simple and curative. If the calculus is within the hilum of the submandibular gland, complete excision of the gland is curative and is done when symptoms are unacceptable or when frequent infections occur. For the parotid gland also, an attempt at conservative therapy is prudent. If recurrent infections occur, however, a parotidectomy should be done. In cases in which only the calculus is removed, the recurrence rate may be as high as 18% because the underlying cause, which is unknown, has not been corrected.

Cystic Lesions

True cysts of salivary tissue are unusual and most occur in the parotid, where they account for 2% to 5% of all parotid lesions. Cysts may be congenital—of which there are three types—or acquired. The dermoid cyst consists of keratinizing squamous epithelium with associated skin appendages and is treated by complete removal with preservation of the facial nerve. The congenital ductal cyst is generally seen in infancy. No therapy is required unless repeated infections occur.[79]

Cysts of the first branchial groove account for less than 1% of all branchial arch anomalies. There are two types: type I is ectodermal and is a duplication anomaly of the membranous external auditory canal; type II is ectodermal and mesodermal and is a duplication anomaly of the membranous and cartilaginous external auditory canal. A type I cyst typically occurs posterior, inferior or anterior to the ear and may bear any relationship to the facial nerve. Prior infection, with or without incision and drainage, may mask the true nature of the lesion. Complete excision during a quiescent period, with preservation of the facial nerve, is curative. A type II lesion may occur from the preauricular area to the hyoid bone. Regardless of the location, the tract is intimately associated with the facial nerve. Again, frequent prior infections may obscure the true lesion. As with type I lesions, excision during a quiescent period, with preservation of the facial nerve, is curative.

Acquired cysts may be due to neoplasms, a benign lymphoepithelial lesion, trauma, parotitis, calculi, duct obstruction or mucus extravasation.[80] Further, the presence of a cyst does not preclude the possibility of a neoplasm, especially a pleomorphic adenoma, an adenoid cystic carcinoma, a mucoepidermoid carcinoma or papillary adenocystoma lymphomatosum (War-

TABLE 8.—*Nonneoplastic, Noninflammatory Causes of Salivary Enlargement*

Nutritional Deficiency
Hypoproteinemia
Pellagra
Beriberi
Hypovitaminosis A
Generalized malnutrition
Obesity
Metabolic or Endocrine Abnormalities
Any malabsorption disorder
Pregnancy
Lactation
Menopause
Diabetes mellitus
Hypothyroidism
Testicular atrophy
Uremia
Alcoholic cirrhosis
Other
Drugs
Pneumoparotitis
Sialodochitis fibrinosa (Kussmaul's disease)

thin's tumor). These are the neoplasms most commonly cystic and are the most common salivary gland neoplasms. For an acquired cyst with an identifiable underlying cause, the latter should be treated first. If that fails, the cyst should be excised. Mucoceles and mucus-retention cysts usually involve the minor salivary glands and most commonly occur in the lips, buccal mucosa and ventral tongue. Mucus-retention cysts are true cysts with an epithelial lining and result from partial duct obstruction. Complete duct obstruction leads to glandular atrophy.[81] Mucoceles do not possess an epithelial lining and are not true cysts. Instead they represent mucus extravasation into the soft tissue. Treatment is by excision or marsupialization if treatment is required. A simple ranula is a mucus-retention cyst of the sublingual gland.

Trauma

Direct injuries of note usually involve a penetrating injury that lacerates the parotid duct. Any penetrating injury to the cheek posterior to the anterior border of the masseter muscle should be suspected of causing a duct injury. If the duct cannot be identified in the wound, a probe should be passed into the duct transorally and located in the wound. This should allow assessment of the duct. If the duct has been transected, the optimum treatment is immediate end-to-end anastomosis over a polyethylene catheter with size 9-0 sutures. The catheter is sutured in place to the buccal mucosa and removed in two weeks. If the proximal end of the transected duct cannot be readily identified, the wound should be carefully dried and the gland compressed. This will often produce enough saliva from the cut end of the duct to allow its identification. If primary anastomosis is impossible but the proximal duct is long enough, the duct may be sutured directly to the buccal mucosa through a puncture wound. If the proximal duct is too short, it may be ligated. This will usually lead to atrophy of the gland, although infection or a salivary-cutaneous fistula may result.

Occasionally a duct injury is missed only to become manifest several days later as a swelling below a sutured wound. In this situation, the wound must be opened and the duct identified and repaired.

Laceration of the parenchyma, in isolation, can usually be managed conservatively. Generally, merely closing the parenchyma and capsule with a few interrupted sutures will suffice. A salivary-cutaneous fistula may develop, but will usually heal with repeated aspiration and a pressure dressing. Resolution often takes 7 to 14 days, by which time the traumatized ductal system will have reopened. Persistence of a fistula strongly suggests duct obstruction in addition to the parenchymal injury.[82] Sialography should be done to investigate this. If ductal obstruction is found, repair should be carried out if possible. If not possible and the fistula persists, a tympanic neurectomy may help. Occasionally a salivary-cutaneous fistula can be diverted into the oral cavity. The entire fistulous tract is excised, turned into the oral cavity through the cheek and sutured to the buccal mucosa.[83] If that fails, excision of the gland or irradiation to destroy the gland may be carried out. Sometimes a sialocele develops instead of a fistula, which may occur in the absence of penetrating trauma.[84]

Penetrating injuries may also transect one or more branches of the facial nerve. The facial nerve of any patient who has suffered a penetrating injury to the face should be thoroughly evaluated. If the wound is anterior to a vertical line from the lateral canthus to the mental foramen (a line approximating the anterior border of the masseter muscle) and only a single branch is involved, repair is probably unnecessary. In this instance recovery is likely from distal anastomosing branches. Posterior to this line, repair should be done immediately.

Blunt trauma can also cause contusion, edema or hemorrhage of the gland. Contusions and edema usually resolve without treatment, though temporary duct obstruction may occur. A hematoma, if significant, should be drained before it becomes organized. If not, subsequent fibrosis and scarring may lead to duct obstruction as well as to cosmetic deformity.

In general, injuries to the submandibular or sublingual glands are managed in the same way as those to the parotid. Penetrating injuries other than parenchymal laceration are uncommon because of the protection offered by the mandible. If an injury does not heal satisfactorily, the gland should be excised.

Sialadenosis

Sialadenosis is a nonspecific term used to describe a noninflammatory, nonneoplastic enlargement of a salivary gland, usually the parotid. Some of the causes are listed in Table 8. Salivary gland enlargement is usually asymptomatic.

Bilateral parotid swelling is common in obesity. A complete endocrinologic and metabolic workup should

be done before a diagnosis of fatty hypertrophy is made. This is because obesity is frequently associated with other disorders such as diabetes mellitus, hypertension, hyperlipidemia and menopause. In particular, hypertrophy is frequently associated with diabetes mellitus and has been reported in cases of acromegaly.

Malnutrition is also frequently associated with sialadenosis, but it is also associated with pellagra, cirrhosis, diabetes mellitus and beriberi.[85] In such cases the level of proteinemia is usually from 3 to 6 grams per dl. Sialadenosis has been reported in cases of kwashiorkor (literally, "red boy") and hypovitaminosis A.[86(p321)] The swelling in these conditions is due to acinar hypertrophy.

The association of parotid swelling with alcoholic cirrhosis is well recognized. It is so rare in cases of nonalcoholic cirrhosis that it can be used as a differential diagnostic feature.[87] In alcoholic cirrhosis, parotid enlargement occurs in 30% to 80% of cases. Current evidence suggests the enlargement is based on protein deficiency, and the histologic changes are similar to those seen in malnutrition. In these patients, the salivary output is normal, but the amylase concentration is increased.

As already implied, any disease that disrupts gastrointestinal absorption of nutrients may lead to parotid hypertrophy. Reported diseases include celiac disease, bacillary dysentery, carcinoma of the esophagus, Chagas's disease and ancylostomiasis.[88] Sialadenosis may occur in cases of uremia, hypothyroidism, myxedema, testicular or ovarian atrophy, pregnancy, lactation and chronic relapsing pancreatitis.

The prognosis of sialadenosis is usually good. The parotid glands generally revert to normal following correction of the underlying cause.

Other Noninflammatory, Nonneoplastic Disorders

Thiourea, isoproterenol, methimazole, phenylbutazone, phenothiazine, thiocyanate, iodine compounds and heavy metals may cause salivary gland enlargement.

Pneumoparotitis may result from any factor that increases intrabuccal pressure. It has been reported in glass blowers, following intubation or endoscopy and as an idiopathic event.

Sialodochitis fibrinosa (Kussmaul's disease) consists of a mucus plug obstructing a collecting duct. This usually occurs in a dehydrated patient and occurs as recurrent swelling with associated pain. The appearance of a mucus plug at the duct orifice is diagnostic. Treatment consists of gentle massage and sialagogues to extrude the plug, in addition to rehydration where appropriate.

Occasionally attention is directed to the salivary glands because of uncontrolled drooling. This generally occurs in neurologically damaged patients. A number of treatments have been advocated. Good results have been reported with bilateral tympanic neurectomy and with submandibular duct relocation. Satisfactory results have also been reported with parotid duct relocation. A more aggressive approach consists of relocating both parotid ducts combined with excising both submandibular glands. In general, drooling should be treated in a progressive manner, with each additional procedure indicated only by failure of the preceding procedure. Radiation should be reserved for operative failures to avoid side effects of xerostomia and increased dental caries, which can be significant management problems in themselves in these patients.

Cheilitis glandularis is an uncommon disease characterized by enlarged labial salivary glands, which secrete a clear, thick, sticky mucus.[89] The glandular hypertrophy may cause eversion of the lower lip. Vermilionectomy is generally curative.

Necrotizing sialometaplasia is a disease of cryptogenic origin, although some cases appear to occur as a reaction to injury. It generally begins as a mucosal ulceration in the hard palate, but may occur anywhere salivary tissue is found. There is a male predominance. It was first reported in 1973,[90] and its importance lies in the fact that it can be mistaken for squamous cell or mucoepidermoid carcinoma clinically and histologically. The lesion is always self-healing and requires no treatment other than biopsy.

Neoplasms

A thorough discussion of neoplasms is beyond the scope of this article. Briefly, salivary gland neoplasms represent less than 3% of all tumors. In all, 75% to 85% occur in the parotid; 80% of parotid, 65% of submandibular, 50% of minor salivary gland and 20% of sublingual gland tumors are benign. There is no significant sex distribution in whites, but nonwhite women have an increased incidence over nonwhite men.

Most benign and malignant tumors appear as an asymptomatic mass below intact skin or mucosa. The growth rate varies and 80% of parotid tumors arise in the caudal aspect of the superficial lobe. Thus every subcutaneous mass in the region of the inferior attachment of the ear should be considered a probable parotid neoplasm.

The basic treatment of benign tumors is complete excision with a cuff of normal tissue around the tumor. For parotid tumors, this means parotidectomy with preservation of the facial nerve.

The behavior of salivary neoplasms was best described by Ackerman and del Regato: "The usual tumor of salivary gland is a tumor in which the benign variant is less benign than the usual benign tumor and the malignant variant is less malignant that the usual malignant tumor."[91] Therefore treatment programs are best evaluated after 20 years rather than five or ten years. For instance, it was once felt that distant metastasis from malignant salivary tumors was uncommon. It is now clear that as the length of follow-up increases, so does the incidence of distant metastasis. The lungs are the most common site, followed by the bones.

The only known risk factors for malignant salivary

tumors is prior irradiation[92] and prior breast cancer in women.[93]

The treatment of malignant salivary neoplasms depends on the histologic type and the clinical stage at presentation. The general tendency at present is to do less aggressive surgical procedures, combined with a more liberal use of postoperative irradiation. Irradiation alone is never the optimum treatment choice.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Hyperthermia Treatments for Cancer

QUESTION:

Are hyperthermia treatments for cancer considered accepted medical practice or are they investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on Internal Medicine, Otolaryngology/Head and Neck Surgery and Radiology, hyperthermia remains an investigational treatment for cancer. Several studies in animals and in humans have shown that hyperthermia may be associated with cancer regression, particularly in the treatment of superficial neoplasms. However, the safe application of hyperthermia, the use of local versus systemic heating techniques and the combination of hyperthermia with other antitumor modalities, such as radiotherapy and chemotherapy, require further investigation. There are no clear indications for hyperthermia as a standard modality in conventional cancer treatment.

Though it may prove to have practical application in the future, hyperthermia treatment for cancer should be conducted under research protocols in centers where the resources exist to properly evaluate the results of this therapy. Research is now being done at a number of institutions in the United States.